Pancreatic Cancer

In 2003, an estimated 30,700 new cases were diagnosed and 30,000 deaths attributable to pancreatic cancer were expected to occur (ACS 2003). Since 1980, incidence rates of pancreatic cancer have declined for men but remain stable for women. In parallel, mortality has decreased by 0.9 percent per year during the past 20 years among men, but has increased slightly among women. One proposed explanation for this trend is a lagged relationship between the prevalence of cigarette smoking and mortality from pancreatic cancer (Weiss and Bernarde 1983). The epidemiologic study of pancreatic cancer is hampered by poor survival rates, which reflect diagnoses at a late or advanced stage of the disease and the difficulty of surgical treatment. The median time from diagnosis to death is about three months, so persons diagnosed with pancreatic cancer may not be alive to participate in case-control studies.

Conclusions of Previous Surgeon General's Reports

The 1972 Surgeon General's report (USDHEW 1972) noted that epidemiologic evidence demonstrates a significant association between cigarette smoking and cancer of the pancreas. In 1979, the Surgeon General's report (USDHEW 1979) indicated that a dose-response relationship between cigarette smoking and pancreatic cancer had been demonstrated. Cigarette smoking was regarded as a contributing factor to pancreatic cancer in both the 1982 (USDHHS 1982) and 1989 (USDHHS 1989) reports. The 1982 report concluded, "Cigarette smoking is a contributory factor in the development of pancreatic cancer. . . .The term 'contributory factor' by no means excludes the possibility of a causal role for smoking in cancers of this site" (p. 7). The 1989 report estimated that 29 percent of pancreatic cancer deaths in men and 34 percent in women could be attributed to smoking. The 1990 report stated that "there is a weak, but consistently observed, association between smoking and pancreatic cancer and that former smokers experience a lower risk of pancreatic cancer than current smokers" (USDHHS 1990, p. 155).

Biologic Basis

Most pancreatic cancers arise in exocrine cells lining the pancreatic ductules. Animal models show that exposures to nitrosamines cause ductlike adenocarcinomas. Similar invasive tumors are produced by feeding the tobacco-specific N-nitrosamine, NNK, to rats (Rivenson et al. 1988). *K-ras* mutations occur in some experimental models of pancreatic cancer. For humans, there is now a large body of evidence that mutations in cellular proto-oncogenes and tumor suppressor genes are important events in pancreatic carcinogenesis. The highest frequency of *ras* mutations has been found in case series of adenocarcinoma of the pancreas. Numerous lines of evidence suggest that *K-ras* mutations are an early and key event in the pathogenesis of pancreatic cancer (Anderson et al. 1996). Investigations of *K-ras* mutations in pancreatic cancer show that the odds of mutation were significantly higher among smokers compared with nonsmokers in several but not all studies (Nagata et al. 1990; Hruban et al. 1993; Malats et al. 1997). Because *ras* mutations appear to be strongly related to cigarette smoking in other malignancies, this association adds support to a causal relationship between smoking and pancreatic cancer. Other potential mechanisms are supported by animal studies, which show that nitrosamines administered parenterally (any way except by mouth) or in drinking water experimentally induce pancreatic cancer (Rivenson et al. 1988). Tobacco-specific carcinogens

may reach the pancreas through the blood or through refluxed bile that is in contact with the pancreatic duct.

In addition to the nitrosamines that are present in high levels in cigarette smoke, aromatic amines also may play a role in pancreatic carcinogenesis. These agents require metabolic activation, probably in the liver or pancreas, to bind to DNA and cause mutations.

Epidemiologic Evidence

Since the association between smoking and pancreatic cancer was last considered in the Surgeon General's reports, substantial new evidence has been reported from both cohort (Table 2.16) and case-control studies (Table 2.17). The findings of these two types of studies are consistent in showing that smoking is associated with increased risk and that the risk increases with the number of cigarettes smoked. The cohort design has the advantage of prospective ascertainment of smoking, before the diagnosis of pancreatic cancer, but only the largest cohorts have substantial numbers of cases. Some of the case-control studies include large numbers of cases, but this approach is weakened by the need to use surrogate respondents for ill or deceased index cases. Alcohol, the principal potential confounding factor, was considered in many of the studies.

Studies conducted around the world provide consistent evidence for increased risk in smokers compared with lifetime nonsmokers. The RR estimates increase with pack-years or number of cigarettes smoked daily. At the highest levels of smoking, the RRs range from three up to five. Risks tend to be lower for former smokers than for current smokers.

Evidence Synthesis

There is now substantial observational evidence on smoking and cancer of the pancreas. Studies of case-control and cohort designs conducted around the world consistently show an increased risk for pancreatic cancer in smokers compared with lifetime nonsmokers. There is evidence for a dose-response relationship of risk with the amount smoked, and evidence that risk declines after quitting. New observations in *ras* mutations in pancreatic cancer further support a causal role for smoking, and pancreatic malignancy can be produced in rats with the tobacco-specific N-nitrosamine, NNK.

In 1986, IARC concluded that smoking causes cancer of the pancreas (IARC 1986). Since that report was published, many more studies support these causal links. In 2002, IARC again concluded that smoking causes cancer of the pancreas and that the risk for pancreatic cancer increases with the duration of smoking and the number of cigarettes smoked daily; the risk remains high after allowing for potential confounding factors such as alcohol consumption; and the risk decreases with increasing time since quitting smoking (IARC 2002).

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and pancreatic cancer.

Implications

Unfortunately, little can be done therapeutically once pancreatic cancer is diagnosed. Smoking prevention and cessation are the only potentially effective strategies for reducing the occurrence of pancreatic cancer.

Bladder and Kidney Cancers

Incidence and mortality rates from bladder cancer vary by gender, race, ethnicity, and age. Bladder cancer incidence rates declined significantly during the 1990s. In 2003, an estimated 57,400 new cases were diagnosed, and an estimated 12,500 deaths were expected to occur (ACS 2003). Overall, bladder cancer incidence is about four times higher in men than in women, and two times higher in whites than in blacks (Ries et al. 2003). Since the 1970s, the mortality rates for bladder cancer have decreased significantly in both whites and blacks.

Cancer can arise in the kidney as renal cell carcinoma or adenocarcinoma, or as a transitional cell carcinoma in the renal pelvis. Transitional cell carcinomas can also occur in the ureters that carry urine to the bladder. The incidence of kidney cancer (including the renal pelvis) is lower than that of bladder cancer, and is higher in men than in women, but the gender difference is less marked than for bladder cancer (Ries et al. 2003). In 2003, an estimated 31,900 new cases were diagnosed and 11,900 deaths were expected to occur (ACS 2003).

Conclusions of Previous Surgeon General's Reports

A relationship between smoking and bladder cancer was noted in the 1964 Surgeon General's report (USDHEW 1964). The 1972 report (USDHEW 1972) concluded that epidemiologic studies demonstrate a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. Further, the report noted that the risk of developing bladder cancer increases with the number of cigarettes smoked. The 1979 report (USDHEW 1979) concluded that cigarette smoking acts independently of and synergistically with other factors to increase the risk of bladder cancer. The 1980 report (USDHHS 1980) noted a dose-response relationship between cigarette smoking and the risk of bladder cancer, and the 1990 report (USDHHS 1990) concluded that smoking causes bladder cancer. Cigarette smoking may account for 30 to 40 percent of bladder cancer cases (USDHHS 1982), and successfully quitting smoking before 50 years of age reduces the risk by about 50 percent after 15 years, in comparison with continued smoking (USDHHS 1990).

Previous Surgeon General's reports summarized evidence regarding kidney cancer in 1982 and 1989. The 1982 report concluded that cigarette smoking is a contributory factor in the development of kidney cancer (USDHHS 1982). The 1989 report indicated a positive association between smoking and kidney cancer, with a RR ranging from 1.0 to more than 5.0 (USDHHS 1989). The risk increased with the number of cigarettes smoked and with the duration of smoking in both men and women.

Biologic Basis

Many products of metabolized components of tobacco smoke are cleared from the body through the kidneys and urine, thus exposing the kidney and bladder to these carcinogenic agents and their metabolites. N-nitrosodimethylamine, a substance found in cigarette smoke, causes kidney tumors in a number of animal models (Shiao et al. 1998). In humans, the urine of smokers has increased mutagenic activity, implying a potential to change the DNA of epithelial cells (Yamasaki and Ames 1977). An analysis of tissue samples from 89 renal cell carcinomas indicated that *p53* mutations identified in these malignancies were similar to those identified in bladder cancers (Bringuier et al. 1998). This observation points to smoking as a shared etiologic factor for cancers of both sites.

Epidemiologic Evidence

Increased risks for cancers of the bladder, kidney, renal pelvis, and ureter have been documented for both male and female smokers. Cigarette smoking is well established as a cause of bladder cancer, with results from approximately 30 case-control studies and 10 prospective cohort studies supporting this relationship (Silverman et al. 1996). The risk increases with the number of cigarettes smoked and the duration of smoking, and declines after smoking cessation. For kidney cancer, a number of studies have shown a dose-response relationship with the number of cigarettes smoked in men and women. Further, the risk

associated with cigarette smoking declines significantly with years of cessation (McLaughlin et al. 1996). Results for renal pelvis and ureter cancer are somewhat stronger, and cigarette smoking accounts for most of these cancers in the United States (70 to 82 percent in men and 37 to 61 percent in women) (McLaughlin et al. 1996).

Recent epidemiologic studies confirm these earlier findings. The 40-year follow-up study of the British physicians cohort shows increasing risks of bladder cancer with an increase in the number of cigarettes smoked per day, and lower risks among former smokers compared with current smokers (Doll et al. 1994). Likewise, the 26-year follow-up of the U.S. veterans cohort shows increasing risks of bladder and kidney cancers with higher numbers of cigarettes smoked. Men smoking more than 40 cigarettes per day had a twofold increase in the risk of bladder and kidney cancers (McLaughlin et al. 1995a). The risks for renal-cell cancer are present in both men and women, although of a lesser magnitude than that observed for transitional-cell tumors of the renal pelvis, where risks resemble those observed for bladder cancer.

The international renal-cell cancer study conducted in Australia, Denmark, Germany, Sweden, and the United States also showed an increase in cancer risks with increasing intensity and duration of smoking (McLaughlin et al. 1995b). This case-control study included 1,050 men and 682 women with renal cell cancer. Long-term quitters experienced a reduction in risk of about 25 percent compared with current smokers.

Evidence Synthesis

The urinary tract is exposed to tobacco carcinogens as they are cleared from the body through the kidneys. In fact, urine of smokers is more mutagenic than that of nonsmokers. Accumulated evidence shows a consistent relationship between cigarette smoking and bladder and kidney cancer risks, a dose-response relationship with the number of cigarettes smoked, and a reduction in risk after successful cessation. In the general population, there are no specific potential confounding factors that need to be considered. Both cohort and case-control studies have found a relationship between smoking and these types of cancer. Finally, in 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the kidney (renal cell carcinoma) (IARC 2002).

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and renal cell, renal pelvis, and bladder cancers.

Implication

Smoking is an established cause of bladder cancer and kidney cancer, and a substantial number of cases could be prevented with smoking prevention and cessation.

Cervical Cancer

Cancer of the cervix is one of the leading causes of morbidity and mortality in women throughout the world. In the United States, rates have declined substantially during the past 50 years, reflecting in part a success of screening. In 2003, an estimated 12,200 new cases of cervical cancer were diagnosed, and an estimated 4,100 women were expected to die from this cancer (ACS 2003). From 1996–2000, the incidence in black women (7.0 per 100,000) was higher than in white women (4.7 per 100,000) (Ries et al. 2003). As cervical cancer screening with Papanicolaou smears has become more widespread, the diagnosis of carcinoma in situ has become far more common, and fortunately, invasive carcinoma of the cervix less common.

Cervical cancer is closely linked to sexual behaviors and sexually transmitted infections with human papilloma virus (HPV) (Bosch et al. 2002). In fact, HPV is now considered to be a necessary cause of cervical cancer. Women who begin having sex at a younger age, who have had many sexual partners, or whose

partners have had many partners are at a higher risk of developing this disease, likely through increased risk for HPV infection. Against this background, the principal epidemiologic challenges have been to separate the effects of cigarette smoking from the risk factor profile associated with low socioeconomic status, which currently is strongly associated with smoking, and to explore possible causal pathways by which smoking may act with HPV in causing cervical cancer.

Conclusions of Previous Surgeon General's Reports

The topic of smoking and cancer of the uterine cervix was first reviewed in the 1982 Surgeon General's report (USDHHS 1982), which concluded that further research was necessary to define whether there was an association between cigarette smoking and cervical cancer. Subsequently, the 1989 report (USDHHS 1989) reviewed more than 15 epidemiologic studies consistently showing an increased risk for cervical cancer in cigarette smokers. Supportive biochemical studies that have detected products of cigarette smoke in cervical mucosa provided a plausible biologic basis for the relationship between cigarette smoking and cervical cancer (USDHHS 1989).

The 1990 report (USDHHS 1990) examined changes in cervical cancer risks after smoking cessation. In the studies that were reviewed, the RR of cervical cancer among current smokers compared with persons who had never smoked ranged from 1.0 to 5.0. After the first year of not smoking, former smokers had lower cervical cancer risks than continuing smokers. The report concluded that the observed diminution in risk after cessation lends support to the hypothesis that smoking is a contributing cause of cervical cancer.

The 2001 report on women and smoking (USDHHS 2001) concluded that smoking has consistently been associated with an increased risk of cervical cancer. It reviewed a large number of case-control studies of invasive cervical cancer and cervical intraepithelial neoplasia, finding smoking to be associated with increased risk in most. However, the report also concluded that the extent to which this association is independent of HPV infection is uncertain. The 2001 report also noted substantial advances in understanding the biology of cervical cancer, notably the role of HPV in carcinogenesis.

Biologic Basis

During the two decades that the Surgeon General's reports have considered smoking and cervical cancer, there have been substantial advances in understanding the role of HPV in causing this malignancy. In almost all cases, HPV DNA can be identified in the tissue, implying that HPV is necessary to cause cervical cancer (Bosch et al. 1995; Walboomers et al. 1999). In the current pathogenetic model for cervical cancer, smoking might act to increase the rate at which malignancy develops in women with persistent infection or possibly to increase the risk for persistent infection.

A range of evidence supports a possible causal association between cigarette smoking and cervical cancer. Cervical mucous in smokers is mutagenic (Holly et al. 1986) and contains nicotine (McCann et al. 1992) and the carcinogen NNK (Prokopcyzk et al. 1997). DNA adducts reflecting damage to DNA by tobacco products were significantly higher in cervical biopsies of smokers compared with nonsmokers (Phillips and Shé 1994). The adducts detected were consistent with tobacco smoking based on comparisons with tobacco-related adducts found in other tissues. Similar results were reported by the same investigators in a second sample of women undergoing a colposcopy or hysterectomy (Simons et al. 1994). Further studies of DNA adduct formation in normal and HPV-16 immortalized human epithelial cervical cells in cultures show that HPV-16 immortalized cells had significantly greater levels of adducts than did normal cells (Melikian et al. 1999). In vitro model systems also have been used to show that smoking may have an effect on the progression of HPV-initiated carcinogenesis of cervical cancer (Nakao et al. 1996).

Epidemiologic Evidence

As an understanding of the role of HPV in causing cervical cancer has advanced, the approach taken in epidemiologic investigations of smoking has also evolved. In the earliest studies, which antedated any consideration of HPV, smoking was treated as a potential independent risk factor, and possible confounding by indicators of sexual behavior was considered (Winkelstein 1977). As the role of HPV was recognized, investigators attempted to control for HPV by introducing indicators for HPV positivity into risk models

Evidence Synthesis

Strong biologic evidence supports a mechanism for direct action of tobacco smoke components on the epithelial cells of the cervix. DNA adducts isolated from cervical cells reflect tobacco exposures among smokers. A large body of epidemiologic evidence supports a positive relationship between smoking and cervical cancer. Smoking has consistently been associated with higher risks of cervical cancer that increase with the duration of smoking and the number of cigarettes smoked per day (USDHHS 2001). Similar associations have been observed for premalignant lesions. Until recently, few studies appropriately considered HPV exposure and infection. HPV is now recognized as a likely contributor to the etiology of most cases and that the risk of smoking is most appropriately assessed in HPV-positive women. The most recent studies consistently show that smoking is associated with an increased risk among HPV-positive women. The increased risk is of a moderate strength and not likely to be explained by confounding by sexual behavior, as all women were HPV-positive in these analyses. Dose-response relationships were also demonstrated. Finally, in 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the uterine cervix (IARC 2002).

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and cervical cancer.

Implication

Further study to refine epidemiologic and mechanistic understanding of the independent association between smoking and HPV infection will clarify the causal association between smoking and cervical cancer.

Evidence Synthesis

Data on the relationship between cigarette smoking and ovarian cancer remain inconclusive. Evidence for patterns of risks with the duration of smoking and time since quitting is limited. Histologic subtypes of ovarian cancer appear to have distinct etiologic factors. Consistent findings suggest that a relationship to cigarette smoking for the mucinous subtype of ovarian cancer is plausible (Marchbanks et al. 2000; Green et al. 2001).

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and ovarian cancer.

Implication

Further research is needed to evaluate risks by histologic subtypes, to evaluate duration of smoking and risk, and to determine the time course of risk following smoking cessation.

Endometrial Cancer

Cancer of the endometrium (uterine corpus) is now the most commonly occurring gynecologic malignancy in women. In 2003, an estimated 40,100 new cases and 6,800 deaths were expected to occur from endometrial cancer (ACS 2003). Incidence rates are higher in white women (14.0 per 100,000) than in black women (10.0 per 100,000), but mortality rates are nearly twice as high for black women (Ries et al. 2003).

Endometrial cancer risks are predominantly determined by various hormonal risk factors: exposures to estrogens from estrogen replacement therapy after menopause, the use of tamoxifen, early menarche or late menopause, nulliparity, and a failure to ovulate (except while taking oral contraceptives). Obesity is also associated with increased risk. Pregnancy and the use of combination oral contraceptive pills (which include both estrogen and progesterone) are each protective against endometrial cancer (Grady and Ernster 1996).

Because of the strong dependence of endometrial cancer risk on exposure to estrogens, separating direct and indirect causal pathways for the effect of smoking on ovarian cancer risk has been difficult. Women who smoke are more likely to be lean and to enter menopause earlier than nonsmokers (Willett et al. 1983). They are thus more likely to take estrogen therapy after menopause and to have more years of estrogen exposure (Pike et al. 1998). Separating causal paths involving smoking from those involving hormonal factors has consequently been complicated.

Conclusions of Previous Surgeon General's Reports

The inverse relationship between cigarette smoking and the risk of endometrial cancer was first noted in the 1989 Surgeon General's report (USDHHS 1989). Endometrial cancer is less frequent in women who smoke cigarettes. The 2001 Surgeon General's report on women and smoking (USDHHS 2001) updated this conclusion by noting that current smoking is associated with a reduced risk of endometrial cancer, although the effect is probably limited to postmenopausal women. The risk of endometrial cancer in former smokers generally appears more similar to that in women who have never smoked.

Biologic Basis

As reviewed in the section on "Breast Cancer" later in this chapter, several lines of evidence support a biologic pathway for cigarette smoking in influencing hormone levels from exogenous estrogen and the risk of hormone-related cancers. Such potential pathways include an altered metabolism as well as a lower production of estrogens because of lower adiposity.

Epidemiologic Evidence

More recent studies continue to show a reduced risk for endometrial cancer in smokers compared with nonsmokers. In a cohort study of participants in the Canadian Mammography Screening Trial, risk was reduced in current smokers compared with lifetime nonsmokers, but only among those smoking 20 or more cigarettes per day (hazard ratio = 0.62 [95 percent CI, 0.42–0.92]) (Terry et al. 2002). Case-control studies in Wisconsin (Newcomer et al. 2001), Washington state (Littman et al. 2001), and Sweden (Weiderpass and Baron 2001) also provide evidence of a reduced risk in smokers compared with nonsmokers (Table 2.18).

Evidence Synthesis

A consistent association between smoking and a lower risk of endometrial cancer has been found. The biologic basis for this association is consistent with the antiestrogenic effect attributed to smoking.

Conclusion

1. The evidence is sufficient to infer that current smoking reduces the risk of endometrial cancer in postmenopausal women.

Implication

Because smoking has numerous adverse health effects as summarized in this report, the modest reduction in the risk of endometrial cancer associated with smoking is far outweighed by the increase in other causes of smoking-related morbidity and mortality.

Stomach Cancer

Despite a major decline in the incidence of stomach cancer in industrialized countries across the last century, gastric carcinoma remains the second most common fatal cancer worldwide (Pisani et al. 1999). An estimated 22,400 new cases and 12,100 deaths from cancer of the stomach were expected to occur in the United States in 2003 (ACS 2003).

Incidence and death rates for stomach cancer vary by race, gender, and ethnicity. Incidence is approximately twice as high among men as among women and higher among nonwhites than whites. A substantial variation of incidence is evident among both men and women, respectively, across various racial and ethnic groups: Asian/Pacific Islanders (23.0 and 12.8), blacks (19.9 and 9.9), Hispanics (18.1 and 10.0), American Indians/Alaska Natives (14.4 and 8.3), and white non-Hispanics (10.0 and 4.3). In the United States, the median survival of persons with stomach cancer is less than one year after diagnosis, although the relative five-year survival rate has increased slightly from 15.1 percent for patients diagnosed in 1975 to 22.5 percent for patients diagnosed in 1992 (Ries et al. 2000a, 2003).

Internationally, death rates from stomach cancer vary nearly 100-fold across countries (IARC 2003). Stomach cancer is the most common malignancy in China and in parts of eastern Asia and Latin America (Parkin et al. 1999; Pisani et al. 1999). Mortality rates have been decreasing worldwide but are as high as 50 per 100,000 among men and 26 per 100,000 among women in the highest risk countries (IARC 2003).

Assessments of the independent contribution of cigarette smoking to the development of stomach cancer are complicated by two factors. First, the background occurrence of stomach cancer decreased globally during much of the twentieth century for reasons unrelated to changes in cigarette smoking. This decline is exemplified by the falling mortality rate from stomach cancer in the United States since 1930, when cause-specific national mortality statistics first became available (Figure 2.6) (Greenlee et al. 2000). The age-adjusted mortality rate (per 100,000) decreased 85 percent in men and 90 percent in women between 1930 and 1997. Figure 2.6 also shows the increase in per capita use of manufactured cigarettes that began in the early 1900s and persisted through 1963 (Giovino et al. 1994), coinciding with much of the decrease in stomach cancer mortality. The main factors proposed to account for the decline in stomach cancer are the introduction of refrigeration (with the resultant increased availability of fresh fruits and vegetables and reduced consumption of salted, smoked, and pickled foods), improved sanitation, and the introduction of antibiotic therapy (reducing chronic *Helicobacter pylori* (*H. pylori*) infections) (Nomura 1996). It has been challenging to identify the contribution to stomach cancer risk from cigarette smoking in the context of large temporal changes in other apparently important risk factors.

A second challenge in determining whether cigarette smoking causes stomach cancer is that the gastric cancers at different subsites appear to differ etiologically, yet are combined in most epidemiologic studies. Subsites of stomach cancer usually are not considered in mortality studies, because death certificates seldom record the histology or location of the tumor within the stomach. The predominant type of stomach cancer observed in incidence registries in the United States and Europe has changed over time, particularly among men. The incidence of cancers of the gastric cardia subsite, occurring near the junction of the esophagus with the stomach, increased by 4.3 percent annually among men in United States SEER areas between 1976 and 1987 (Devesa and Fraumeni 1999). A similar increase in gastric cardia cancers has been observed in Europe (Golematis et al. 1990; Craanen et al. 1992; Botterweck et al. 2000), at the same time that the incidence of cancers of the gastric antrum, corpus, or fundus (termed noncardia cancers) has been decreasing worldwide. The decline in noncardia cancers accounts for most of the global decline in stomach cancer. As a consequence of these opposing trends, tumors of the gastric cardia now compose about one-third of all stomach cancers among white men in the United States (Blot et al. 1991).

Conclusions of Previous Surgeon General's Reports

Stomach cancer has not been classified among the diseases definitely caused by tobacco smoking by the Surgeon General (USDHEW 1964, 1974; USDHHS 1982, 1989a) or IARC until the most recent monographs

"smoking," "gastric neoplasms," and "stomach neoplasms," and by examining references cited in published original and review articles (Trédaniel et al. 1997).

Nine cohort studies (Table 2.19) (Nomura et al. 1990; Kneller et al. 1991; Kato et al. 1992; Tverdal et al. 1993; Doll et al. 1994; McLaughlin et al. 1995a; Engeland et al. 1996; Mizoue et al. 2000; ACS, unpublished data) and 11 case-control studies (Table 2.20) (Correa et al. 1985; Jedrychowski et al. 1986; Boeing et al. 1991; Saha 1991; Agudo et al. 1992; Hansson et al. 1994; Ji et al. 1996; De Stefani et al. 1998; Chow et al. 1999; Inoue et al. 1999; Zaridze et al. 2000) have examined the association between cigarette smoking status and incidence of or death from stomach cancer. Current cigarette smokers consistently have higher incidence or death rates than do lifetime nonsmokers in studies of men (Nomura et al. 1990; Kneller et al. 1991; Tverdal et al. 1993; Doll et al. 1994; McLaughlin et al. 1995a; Engeland et al. 1996; Mizoue et al. 2000; ACS, unpublished data) and men and women combined (Kato et al. 1992); this finding is less consistent in studies of women (Table 2.19) (Tverdal et al. 1993; Engeland et al. 1996; ACS, unpublished data). The average RR estimate among current smokers compared with lifetime nonsmokers across all of the studies in Tables 2.19 and 2.20, weighted by the number of cases, is 1.6 (1.7 in men and 1.3 in women). Relative risk estimates above 2.0 are seen in several studies of Japanese (Nomura et al. 1990; Kato et al. 1992; Inoue et al. 1999; Mizoue et al. 2000) and other populations with above average risks of stomach cancer (Kneller et al. 1991; Tverdal et al. 1993; De Stefani et al. 1998).

Former smokers have lower incidence or death rates for stomach cancer than do continuing smokers in most studies of men (Tables 2.19 and 2.20) (Nomura et al. 1990; Kneller et al. 1991; Tverdal et al. 1993; Doll et al. 1994; McLaughlin et al. 1995a; Ji et al. 1996; De Stefani et al. 1998; Chow et al. 1999; Inoue et al. 1999; Zaridze et al. 2000; ACS, unpublished data), although one study found a higher risk for former smokers in men and women (Kato et al. 1992). The average RR estimate in former smokers across all studies combined is 1.2 (1.2 in men and 1.3 in women).

Among current smokers, most studies document only a small increase in the risk for stomach cancer with an increasing number of cigarettes smoked per day (Tables 2.21 and 2.22) or years of smoking (Table 2.23). Two prospective studies that do show some gradient of an increased risk with a greater number of cigarettes smoked are the reports by Kneller and colleagues (1991) from Norway and McLaughlin and colleagues (1995a) on United States veterans. The tests for a trend presented in Tables 2.21 and 2.22 are taken from the original papers and do not always specify whether lifetime nonsmokers were excluded from the trend calculations. No significant trend is observed with either the number of cigarettes smoked per day (Table 2.22) or number of years of smoking (Table 2.23) in CPS-II (ACS, unpublished data).

Among former smokers, the risk of stomach cancer consistently decreases below that of continuing smokers with the number of years since cessation (Table 2.24). This trend is clearest in the studies with the largest number of former smokers (De Stefani et al. 1998; ACS, unpublished data). The risk of stomach cancer among former smokers approaches that of lifetime nonsmokers approximately 20 years after quitting.

The epidemiologic studies that have separated cancers of the gastric cardia from noncardia cancers suggest that cancers at both subsites are associated with cigarette smoking (Table 2.25). Two case-control studies (Kabat et al. 1993; Gammon et al. 1997) report stronger associations between smoking and cancers of the gastric cardia than between smoking and noncardia cancers. However, the evidence relating smoking to specific types of stomach cancer is limited (Nomura 1996), as most studies have not been analyzed by anatomic or histologic subsites.

Evidence Synthesis

A large decrease in stomach cancer incidence and death rates occurred in the United States during the time per capita cigarette smoking increased steeply. The timing of these trends and the continuing decrease in gastric cancer incidence and mortality worldwide suggest that cigarette smoking is not, by itself, a major independent cause of stomach cancer. It nevertheless remains possible that cigarette smoking is an important factor in the pathogenesis of both cardia and noncardia stomach cancers.

Many large, well-conducted epidemiologic studies consistently report higher incidence or death rates for stomach cancer among current cigarette smokers than among lifetime nonsmokers. Studies that distinguish between cancers of the gastric cardia and those elsewhere in the stomach generally find that smoking is associated with both sites. Persons who stop smoking have a lower risk of stomach cancer than those who continue. The risk among former smokers diverges progressively away from that of continuing smokers and toward that of lifetime nonsmokers as time elapses after cessation. Among current smokers, the risk of stomach cancer is not strongly associated with either years of smoking or the number of cigarettes smoked per day. In 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the stomach (IARC 2002).

Cigarette smoking may increase the infectivity or add to the pathogenicity of *H. pylori*, a known cause of noncardia stomach cancer. The prevalence of *Helicobacter* infections is inconsistently reported to be higher among cigarette smokers than among lifetime nonsmokers in some studies. The eradication of *H. pylori* infections using antibiotics was more difficult in smokers than nonsmokers in several studies. An *H. pylori* infection in combination with cigarette smoking is associated with more frequent ulcerations (gastric and duodenal combined) (Martin et al. 1989), the progression to metaplasia (Jedrychowski et al. 1993, 1999), and/or gastric cancers (Zaridze et al. 2000) than is an *H. pylori* infection alone. Cigarette smoking is also thought to deplete the plasma and serum concentrations of certain micronutrients that may protect against *Helicobacter* infections or gastric neoplasia.

Two important limitations of most of the epidemiologic studies are that few studies have measured infections with *H. pylori* and cigarette smoking in the same people, and studies have not consistently distinguished between gastric cardia and noncardia cancers. Such information is needed to examine the separate and joint effects of cigarette smoking and an *H. pylori* infection on the main subtypes of stomach cancer. The interaction between smoking and *H. pylori* may vary across different subtypes of gastric cancer. Some evidence suggests that *H. pylori* infections may be negatively associated with cancers of the gastric cardia but positively associated with noncardia gastric cancers (Hansen et al. 1999). The critical exposure for noncardia cancers may be the combination of an *H. pylori* infection and cigarette smoking. If so, then conventional dose-response analyses may misclassify the duration or intensity of the relevant exposure by considering one or both of these factors separately.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and gastric cancers.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and noncardia gastric cancers, in particular by modifying the persistence and/or the pathogenicity of *Helicobacter pylori* infections.

Implications

With inference of a causal association between current and former cigarette smoking and death from gastric cancers, including stomach cancer among the smoking attributable conditions increases the estimated number of deaths caused by smoking by 3,573 in 1990 in the United States, based on CPS-II. The impact of smoking on gastric cancers may be substantially greater in developing countries where the incidence of and mortality from stomach cancer are higher.

Reductions in smoking could help to counteract the increase in cancers of the gastric cardia occurring in the United States and Europe, especially among men. Further research is needed to assess the combined effects of cigarette smoking and an *H. pylori* infection. Of particular interest is the impact of continued cigarette smoking on the infectivity and pathogenicity of *H. pylori*, and the relationship of smoking and other factors to cancers of the gastric cardia.

Table 2.25 Continued

Study Location/population	Smoking status	Cardia Number of cases/controls	RR	95% CI
	Men and women			
Ye et al. 1999				
	Never smoked	34/512	1.0	
Sweden, 1989–1995 (population controls	Current smokers	25/415	0.9	0.5–1.6
matched for age and gender)	Former smokers	31/237	1.7	1.0–3.1
Lagergren et al. 2000				
	Never smoked	43/325	1.0	
Sweden, 1995–1997 (population controls	Current smokers	95/181	4.5	2.9–7.1
matched for age and gender)	Former smokers	124/314	3.4	2.2–5.2

Colorectal Cancer

Together, cancers of the colon and rectum rank as the third most common cancers and cause of cancer deaths among men and women in the United States (ACS 2003). In 2003, an estimated 105,500 cases of cancer of the colon and 42,000 cases of cancer of the rectum were expected to be diagnosed. That same year, 57,100 deaths from both cancers combined were expected to occur (ACS 2003). In the mid-1990s, the lifetime probability of developing colorectal cancer was estimated to be 5.6 percent in the United States (Greenlee et al. 2000).

Worldwide, colorectal cancer incidence and mortality rates vary more than 10-fold among countries; the highest rates occur in western Europe, North America, Australia/New Zealand, and Japan; and the lowest rates occur in countries with developing economies, particularly in Africa and Asia (Parkin et al. 1999; Pisani et al. 1999). Studies of migrants show that, in immigrants moving from countries where the incidence is low to countries where the incidence is high, incidence rates increase within one generation to approximate rates of the new country, suggesting a strong role for environmental causes (Thomas and Karagas 1987; McMichael and Giles 1988).

The average annual age-adjusted population incidence rate of colorectal cancer per 100,000 in the United States from 1996–2000 was 72.4 in black men, 64.1 in white men, 57.2 in Asian/Pacific Islander men, 56.2 in black women, 49.8 in Hispanic men, 46.2 in white women, 38.8 in Asian/Pacific Islander women, 37.5 in American Indian/Alaska Native men, 32.9 in Hispanic women, and 32.6 in American Indian/Alaska Native women (Ries et al. 2003). Incidence rates are consistently higher among men than among women in all racial and ethnic groups (Ries et al. 2003). Colorectal cancer incidence rates increased from 1973 until 1985 and began decreasing steadily in the mid-1980s; mortality rates increased through 1991 and then decreased rapidly through 1997 (Chu et al. 1994; Ries et al. 2000b). The decrease in both incidence and mortality rates has been larger and began earlier in white women than in white men.

Noncardia			
Number of cases/controls	RR	95% CI	Comments
Distal stomach (intestinal type)			Adjusted for age, gender, geographic area, BMI, socioeconomic status, smokeless tobacco use, and alcohol intake; current/former smokers included pipe/cigar smokers
92/512	1.0		
101/415	1.4	1.0–2.0	
67/237	1.8	1.2–2.7	
Distal stomach (diffuse type)			Adjusted for age, gender, geographic area, BMI, socioeconomic status, smokeless tobacco use, and alcohol intake; current/former smokers included pipe/cigar smokers
61/512	1.0		
46/415	1.3	0.8–2.0	
57/237	2.2	1.4–3.5	
NR	NR	NR	Adjusted for age; gender; education; BMI; reflux symptoms; physical activity; and fruit, vegetable, energy, and alcohol intake; current/former smokers included pipe/cigar smokers

The five-year relative survival rate among whites in the United States is approximately 90 percent when colorectal cancers are diagnosed and treated at the localized stage, but falls below 10 percent when they are diagnosed at the distal stage. Fewer than 40 percent of all cases are diagnosed at the localized stage (Ries et al. 2003). A shift toward an earlier stage at diagnosis occurred among white men and women in the United States between 1975 and 1995 (Troisi et al. 1999), and the resulting improvements in survival have been attributed mostly to the earlier removal of localized carcinomas (Chu et al. 1994; Troisi et al. 1999; Ries et al. 2000b).

Colorectal cancer risk factors include physical inactivity, obesity, and perhaps a diet high in saturated and animal fats and low in vegetables and fruits. These risk factors are still under investigation and uncertainty remains, particularly with regard to the specific dietary factors. The risks also increase for persons with a family history of colorectal cancer or polyps. Factors consistently associated with a reduced risk are the use of aspirin and other nonsteroidal anti-inflammatory drugs, and hormone replacement therapy use among women (Potter 1999).

Colorectal cancer was among the causes of mortality assessed in cohort studies. The hypothesis that prolonged cigarette smoking may contribute to colorectal cancer gained support in the mid-1990s when epidemiologic (particularly cohort) studies reported a higher incidence of adenomatous polyps and/or cancer in long-term smokers (Giovannucci et al. 1994a,b). Uncertainty about the reports of this observed association has primarily come from the possibility of uncontrolled confounding by other lifestyle determinants of risk that are still under study (Doll 1996; Giovannucci and Martínez 1996). Giovannucci and Martínez (1996) and Giovannucci (2001) have provided comprehensive reviews of the literature and the methodologic concerns.

Conclusions of Previous Surgeon General's Reports

Until the 2001 Surgeon General's report on women and smoking (USDHHS 2001), this series of reports had not considered smoking in relation to cancers of the colon and rectum, and colorectal cancers

and timing, beyond smoking status (Giovannucci et al. 1994a,b; Nyrén et al. 1996; Hsing et al. 1998; Chao et al. 2000). Four recent reports from cohort studies have described an increased risk of colorectal cancer incidence and mortality with increased smoking duration in both men and women (Table 2.29) (Giovannucci et al. 1994a,b; Hsing et al. 1998; Chao et al. 2000). The sole exception is the Swedish study of men in whom no increased risk was observed with an increase in smoking duration (Nyrén et al. 1996). The Health Professionals Follow-Up Study (Giovannucci 1994b) reported a significantly increased risk among men who had smoked at least 40 to 44 years (RR = 1.7); the 16-year follow-up of the Nurses Health Study (Giovannucci 1994a) reported an elevated risk in women who had smoked more than 10 cigarettes a day for 35 to 39 years (RR = 1.5); and another cohort of U.S. men (Hsing et al. 1998) found an increased risk after smoking 20 to 29 years (RR = 2.4).

CPS-II found a statistically significant increase in risk of colorectal cancer mortality among male smokers of 30 to 39 years' duration (multivariate RR = 1.3) and among female smokers of 20 to 29 years' duration (multivariate RR = 1.3) (Chao et al. 2000). Controlling for multiple covariates decreased age-adjusted estimates in currently smoking men but had little net effect on age-adjusted estimates in currently smoking women. Results of cohort studies that assess cigarette smoking status only at cohort enrollment may underestimate the true risk among long-term continuing smokers, because some smokers will have quit smoking during the cohort follow-up period.

Two cohort studies of colorectal cancer mortality have found a consistently increasing risk associated with a younger age at smoking initiation (Table 2.30) (Heineman et al. 1995; Chao et al. 2000). The 26-year follow-up of the veterans cohort reported that initiating smoking before 15 years of age was associated with a RR of 1.4 for colon cancer and 1.5 for rectal cancer (Heineman et al. 1995). CPS-II found that currently smoking men and women who began smoking at 15 years of age or younger had an increased risk of death from colorectal cancer (multivariate RR = 1.4 in men and 1.7 in women) (Chao et al. 2000).

Data from CPS-II show that former smokers experience lower colorectal cancer mortality rates compared with continuing smokers (Table 2.31) (Chao et al. 2000). Risk decreases with a younger age at and a greater number of years since smoking cessation; former smokers who quit 20 or more years before the study were not at an increased risk of death from colorectal cancer compared with nonsmokers. Controlling for multiple covariates reduced the age-adjusted risk estimates in former male smokers but increased the risk estimates in former female smokers. The Leisure World cohort also found that men who had quit smoking more than 20 years ago were at a lower risk of colorectal cancer incidence than those who had quit within the past 20 years (Wu et al. 1987). In the multisite case-control study conducted by Slattery and colleagues (1997), risk remained modestly elevated for those former smokers who had stopped for 15 years or more.

Evidence Synthesis

There is now a strong understanding of the sequence of genetic changes that leads from a normal cell to polyp development and then on to malignancy. Evidence points to an effect of smoking on polyp formation and possibly on the development of malignancy. Recent findings of prospective cohort studies suggest that long-term cigarette smoking is associated with an increased risk of colorectal cancer incidence and mortality in both men and women; risk is highest in current cigarette smokers, intermediate in former smokers, and lowest in nonsmokers. In some studies, the risk of colorectal cancer incidence and mortality tends to increase with longer smoking duration and a younger age at smoking initiation, and decreases with a younger age at and a greater number of years since successful smoking cessation, although the effects of these two factors cannot be readily separated because of their inherent correlation.

The aggregate epidemiologic evidence supports the hypothesis by Giovannucci and colleagues (1994a,b) and Giovannucci and Martinez (1996) that a latent period of several decades is necessary for cigarette smoking to increase colorectal cancer incidence or mortality, and that cigarette smoking likely plays a role in early colon and rectum carcinogenesis. This hypothesis is further supported by the association of smoking with adenomas. A number of studies show a greater risk for polyps in smokers compared with nonsmokers, and some show a dose-response relationship

with the number of cigarettes smoked. Under this hypothesis, the early studies of smoking might have missed an association because of insufficient follow-up time for the necessary tumor growth. This phenomenon would particularly apply to women, since the smoking epidemic began later in women than in men in the United States and most other developed countries. The finding of a declining risk following smoking cessation also suggests that cigarette smoking may affect later stages of the carcinogenic process leading to colorectal cancer.

In assessing whether cigarette smoking plays a causal role in colorectal cancer, consideration needs to be given to nutritional or other factors, such as physical activity and participation in colorectal cancer screening, that may confound the association. Not all recent studies have controlled for colorectal cancer risk factors that may be associated with smoking, such as physical inactivity. However, indirect evidence against confounding comes from the consistent finding of a small but statistically significant increase in risk associated with smoking, regardless of the set of covariates adjusted for in an analysis. Among the prospective cohort studies, three adjusted for physical activity or inactivity (Heineman et al. 1995; Chao et al. 2000; Stürmer et al. 2000). CPS-II analyses further adjusted for the use of estrogen replacement therapy (in women) and aspirin or other nonsteroidal anti-inflammatory drugs (Chao et al. 2000), factors that have been consistently associated with a lower risk of colorectal cancer (Thun et al. 1992; Calle et al. 1995; Potter 1999). Three cohort studies (Giovannucci et al. 1994b; Chao et al. 2000; Stürmer et al. 2000) adjusted for some measure of diet, and four studies (Giovannucci et al. 1994b; Hsing et al. 1998; Chao et al. 2000; Stürmer et al. 2000) adjusted for alcohol consumption. The only study of incidence or mortality that adjusted for screening sigmoidoscopy (as well as other variables) in women reported RR estimates similar to CPS-II results for smoking duration and years since quitting (Newcomb et al. 1995).

Adjusting for measured potential confounders for colorectal cancer in CPS-II affected the association with cigarette smoking differently by gender and by smoking status. Such adjustments increased risk estimates for former female smokers, had little net effect on risk estimates for current female smokers, and decreased the risk estimates for men. The slight decrease in adjusted estimates among men was comparable to that reported from the Health Professionals Follow-Up Study (Giovannucci 1994b), which controlled for saturated fat, folate, and dietary fiber and was one of the few studies that reported age- and multivariate-adjusted risk estimates. Although the possibility of residual confounding cannot be completely excluded, the internal consistency of findings and the fact that adjusting for measured potential confounders actually strengthened the association between smoking and colorectal cancer mortality in former female smokers in CPS-II suggest that the observed associations are unlikely to be explained solely by confounding. While the cohort study data are generally consistent with the hypothesis that smoking causes colorectal cancer, the trends of colorectal cancer incidence in the United States appear to be inconsistent. If smoking causes colorectal cancer after a substantial latent period as hypothesized (Giovannucci 2001), then the temporal patterns of smoking across the twentieth century would predict a decline in incidence in men before a decline in women. The opposite pattern has been observed (Ries et al. 2000b). However, other factors such as changes in risk variables and screening practices would also affect trends in incidence rates. Given the relatively modest effect of smoking on colorectal cancer risks, trends in incidence are an insensitive indicator of any trends in the effects of smoking over time.

Cigarette smoking is associated with a diagnosis of colorectal cancer at a more advanced stage of the disease (Longnecker et al. 1989), leading to a poorer prognosis and a lower survival rate in smokers compared with nonsmokers. However, recent cohort studies have reported similar findings of increased risks among smokers for both colorectal cancer incidence and mortality (Giovannucci et al. 1994a,b; Chao et al. 2000). Although no published reports were found on colorectal cancer screening prevalence by cigarette smoking status, the 1990–1994 National Health Interview Surveys (Rakowski et al. 1999) show that compared with lifetime nonsmokers, women who currently smoke are less likely, and those who are former smokers are more likely, to be screened for breast and cervical cancers. Thus, colorectal cancer mortality

studies cannot exclude the possibility that continuing smokers experienced higher death rates from colorectal cancer than did nonsmokers because of less screening and a later stage of disease at diagnosis. However, the statistically significant increase in risk of colorectal cancer mortality among former female smokers in CPS-II argues against appreciable confounding by differential colorectal cancer screening practices, because these women are perhaps the most likely to be screened. CPS-II results were also similar to those of the one study that adjusted for screening sigmoidoscopy (Newcomb et al. 1995). The consistently observed relationship between cigarette smoking and adenomatous polyps, especially large adenomas (Kikendall et al. 1989; Cope et al. 1991; Monnet et al. 1991; Zahm et al. 1991; Lee et al. 1993; Olsen and Kronborg 1993; Giovannucci et al. 1994a,b; Peipins and Sandler 1994; Boutron et al. 1995; Martínez et al. 1995; Longnecker et al. 1996; Nagata et al. 1999; Potter et al. 1999; Almendingen et al. 2000; Breuer-Katschinski et al. 2000; Inoue et al. 2000), also suggests that confounding by screening is unlikely to explain the increased risk observed in studies of colorectal cancer incidence and mortality.

In 2000, about 23 percent of adults in the United States were current cigarette smokers, and 22 percent were former smokers (CDC 2002b). In 2001, 29 percent of high school students were current cigarette smokers (CDC 2002a). If long-term cigarette smoking is a cause of colorectal cancer (one of the most common cancers in western populations), the multivariate-adjusted RR estimates in CPS-II would indicate that about 12 percent of colorectal cancer deaths among men and 12 percent among women in the general population were attributable to smoking.

Cumulative findings from several recent, large prospective studies show an increased risk of colon and rectal cancer after smoking for two or more decades. The temporal pattern of the effects of smoking suggests that it may act in both earlier and later stages of carcinogenesis.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Implications

The aggregate evidence suggests that cigarette smoking may be one of the avoidable factors that causes colorectal cancer. Current and former smoking should be included with other potential risk factors for this disease in clinical and public health settings, and further research should be directed at smoking and colorectal cancer risk.

The possible inclusion of colorectal cancer among the smoking-related cancers would substantially increase estimates of smoking attributable cancers and deaths worldwide. In the United States, the proportion of colorectal cancer deaths in 1997 attributable to any cigarette smoking (based on CPS-II multivariate-adjusted RRs) would be approximately 12.0 percent among men and 12.3 percent among women, corresponding to an estimated 6,800 deaths. Considering past and future trends in cigarette smoking prevalence in the United States (Pierce et al. 1989) and in colorectal cancer incidence and mortality by gender since the 1950s (Chu et al. 1994), further reductions in smoking among adolescents and adults could accelerate and sustain future reductions in incidence and mortality.

Prostate Cancer

Prostate cancer is a leading cause of morbidity and mortality among men in the United States. It is more common in African American men than in white men, and the highest recorded rates in the world are among black men in the United States. In 2003, an estimated 220,900 new cases of prostate cancer were diagnosed, and an estimated 28,900 deaths were expected to occur (ACS 2003). Prostate cancer is the leading cause of cancer incidence among men (ACS 2003).

The risk of prostate cancer increases with age. African American men are at an increased risk, whereas Asian men are at a lower risk than white men. Lower vitamin A consumption and higher animal fat intake may increase the risk (Gann et al. 1994; Le Marchand et al. 1994), while a higher intake of lycopene may decrease the risk (Giovannucci et al. 1995; Giovannucci 1999). Having a vasectomy may be associated with an increased risk of prostate cancer 20 or more years after the procedure (Ross and Schottenfeld 1996). Endocrine factors, including testosterone and insulin-like growth factors, have been implicated in the development of this malignancy (Ross and Schottenfeld 1996; Giovannucci et al. 1997; Chan et al. 1998). Variations in the length of the androgen receptor gene CAG repeat may explain part of the excess risk in African American men (Platz et al. 2000).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports have not addressed the relationship between smoking and prostate cancer.

Biologic Basis

During the last several decades there has been an explosion of epidemiologic studies addressing potential risk factors for this common malignancy, including cigarette smoking. Pathogenic mechanisms that may underlie the relationship between smoking and prostate cancer remain unclear. Carcinogens from tobacco can enter and concentrate in prostate cells (Smith and Hagopian 1981). Compared with men who do not smoke, men who smoke cigarettes have higher circulating levels of hormones formed in the adrenal gland (dehydroepiandrosterone, dehydroepiandrosterone sulfate, cortisol, and androstenedione) as well as testosterone, dihydrotestosterone, and sex hormone-binding globulin (Dai et al. 1988; Khaw et al. 1988; Field et al. 1994). This finding supports a potential mechanism for smoking because prospective epidemiologic studies have shown that testosterone is directly related to prostate cancer incidence and mortality (Nomura et al. 1988; Hsing and Comstock 1993; Gann et al. 1996).

Epidemiologic Evidence

The epidemiologic evidence relating smoking to the risk of prostate cancer has been mixed. Studies addressing disease incidence (which include case-control studies and several cohort studies) show an inconsistent increase in risk (Mishina et al. 1985; Honda et al. 1988; Hayes et al. 1994; van der Gulden et al. 1994), or no association between cigarette smoking and prostate cancer (Weir and Dunn 1970; Ross et al. 1987; Fincham et al. 1990; Talamini et al. 1992). Studies of mortality, largely limited to prospective cohort studies, show an increase in risk directly related to the number of cigarettes smoked. Investigators using different approaches to data analysis have attempted to determine whether this finding reflects a delayed diagnosis and treatment of smokers compared with nonsmokers, residual confounding factors, or a direct effect of tobacco smoke. Two studies found that smokers are more likely than nonsmokers to have their cancers diagnosed at a more advanced stage or histologic grade (Hussain et al. 1992; Daniell 1995).

Hsing and colleagues (1991) analyzed data from the follow-up of nearly 250,000 U.S. veterans and observed increased mortality rates for those who were current smokers at baseline. During 26 years of follow up, approximately 4,600 men died of prostate cancer. Current smokers had a RR of 1.18 (95 percent CI, 1.09–1.28) compared with men who had never smoked, and the risk increased with the number of cigarettes smoked. Men smoking 40 or more cigarettes per day had a RR of 1.51 (95 percent CI, 1.20–1.90) compared with those who had never smoked. In this cohort, risks were higher during the first eight and one-half years of follow-up than during the remainder of the follow-up period, suggesting that recent smoking influenced the risk of prostate cancer mortality.

Evidence Synthesis

The suggestion of elevated risks for mortality and not for incidence (measured either in case-control studies or in prospective cohort studies) supports an association between smoking and prostate cancer mortality. The association between smoking and prostate cancer mortality rates appears to be reduced within 10 years of smoking cessation. The basis for this association is unclear. It might reflect more advanced disease in smokers, but evidence is limited.

If smoking contributed to the etiology of prostate cancer, an association of smoking with incidence would be anticipated, along with an increase in disease-specific mortality, assuming that cancers in smokers and nonsmokers are similar in clinical features.

Conclusions

1. The evidence is suggestive of no causal relationship between smoking and risk for prostate cancer.

2. The evidence for mortality, although not consistent across all studies, suggests a higher mortality rate from prostate cancer in smokers than in nonsmokers.

Implications

Smoking cessation may reduce prostate cancer mortality. Further research is needed to refine this temporal relationship and to quantify the benefits of smoking cessation after diagnosis with prostate cancer.

Acute Leukemia

In 2003, an estimated 21,900 deaths attributable to leukemia and an estimated 30,600 new cases, evenly divided between acute and chronic leukemia, were expected to occur, affecting 10 times more adults than children (ACS 2003). In adults, the most common types of leukemia are acute myeloid (approximately 10,500 cases were diagnosed in 2003) and chronic lymphocytic (approximately 7,300 cases were diagnosed in 2003). Rates of acute myeloid leukemia among adults are higher in males than in females. In children, the most common type of leukemia is acute lymphocytic, accounting for 2,200 cases in 2003 (ACS 2003).

Conclusions of Previous Surgeon General's Reports

The 1990 Surgeon General's report (USDHHS 1990) noted that smoking has been implicated in the etiology of leukemia but the evidence was not consistent, and a conclusion was not reached regarding a possible causal relationship. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that acute myeloid leukemia has been consistently associated with cigarette smoking.

Biologic Basis

Several known leukemogenic substances are contained in cigarette smoke, including benzene and polonium-210 and lead-210 (which emit ionizing radiation). Both benzene and ionizing radiation (NRC 1990) are known causes of human leukemia that are associated with myeloid forms of leukemia and have little, if any, effect on the incidence of chronic lymphocytic leukemia. Radiation also causes acute lymphocytic leukemia in children (NRC 1990). Benzene, classified as a human carcinogen by IARC (1986), induces leukemia both in humans through occupational exposures and in laboratory animal models of this disease. Cigarette smoke is a major source of benzene exposure in the United States, accounting for roughly half of the exposures (Wallace 1996). Among smokers, 90 percent of benzene exposures come from smoking (Wallace 1996).

stronger for the first 16 years of follow-up (RR = 1.6 [95 percent CI, 1.3–1.9]) than in the later 10 years (years 15 to 26 of the follow-up) (RR = 1.1 [95 percent CI, 0.9–1.3]) (McLaughlin et al. 1995a). In these data, the overall risk increased with the number of cigarettes smoked per day.

Cohort studies by Linet and colleagues (1991) and by Mills and colleagues (1990) also found a positive dose-response relationship between the number of cigarettes smoked and risk of leukemia. In the Lutheran Brotherhood Cohort Study, Linet and colleagues (1991) reported 74 deaths from leukemia (30 myeloid, 30 lymphatic, and 14 unspecified leukemia cases) among 17,633 white males followed for 20 years. The risk of total leukemia increased with the number of cigarettes smoked per day. Mills and colleagues (1990) followed 34,000 Seventh-Day Adventists for six years and identified 46 histologically-confirmed cases of leukemia. The group that had smoked the highest number of cigarettes in their lifetime had the highest risk of leukemia. These two cohorts were considerably smaller than the U.S. veterans and ACS studies. Other studies supporting a positive dose-response relationship include some of the case-control studies.

Among the prospective studies, the 20-year follow-up of a cohort of construction workers in Sweden shows no relationship between smoking and leukemia (Adami et al. 1998). In this study, 400 cases of leukemia (including 171 myeloid leukemias) were diagnosed during follow-up. Current smokers had a RR for total leukemia of 1.0 (95 percent CI, 0.8–1.2) compared with workers who had never smoked. Similar null results were also observed for myeloid leukemia (RR = 1.0 [95 percent CI, 0.7–1.4]), and there was no evidence of a trend in risks with the number of cigarettes smoked per day.

Evidence Synthesis

A relationship between former or current smoking and the risk of acute myeloid leukemia is supported by evidence of a consistent dose-response relationship with the number of cigarettes smoked per day. The association of the duration of smoking with the degree of risk and an increase in risk among former smokers suggests that the relationship is not dependent on current smoking, but perhaps on the cumulative effects of cigarette smoking. This relationship is observed across diverse populations. The RR for persons who had ever smoked compared with nonsmokers ranged from 1.3 to 1.5. Among those who smoked more than a pack of cigarettes per day the risk increased twofold. In 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and myeloid leukemia (IARC 2002).

Data from human and experimental animal studies provide evidence of a relationship between smoking and leukemia. Known leukemogens have been identified in cigarette smoke, and specific genetic alterations have been reported in smokers with leukemia. Benzene, a known leukemogen (Heath 1990), is found in cigarettes, and is the strongest known chemical leukemogen (Linet and Cartwright 1996). Polonium-210 and lead-210, alpha particle emitters in cigarette smoke, can reach the bone marrow where stem cells are located (Austin and Cole 1986; NRC 1988).

Korte and colleagues (2000) used risk assessment techniques for low-dose extrapolation to assess the proportion of leukemia and acute myeloid leukemia cases that could be attributed to the benzene in cigarettes. On the basis of linear potency models, these authors concluded that benzene in cigarette smoke contributed between 8 and 48 percent of smoking-induced leukemia deaths in total, and from 12 to 58 percent of smoking-induced acute myeloid leukemia deaths.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and acute myeloid leukemia.

2. The risk for acute myeloid leukemia increases with the number of cigarettes smoked and with duration of smoking.

Implications

The incidence of leukemia may remain elevated even after smoking cessation. Evidence is limited on the temporal pattern of change in risk after cessation, but a rapid decline in incidence has not been observed. Further research is needed to refine the patterns of risk after smoking cessation.

Liver Cancer

There are strong geographic variations in liver cancer incidence around the world. Although liver cancer is a relatively infrequent cause of cancer mortality in the United States, it is a leading cause of cancer deaths in the world (London and McGlynn 1996). In the United States, less than 1.5 percent of incident cancers are primary cancers of the liver and bile ducts. However, cancer of the liver ranks eighth (by deaths) on a worldwide basis, with three-quarters of the cases occurring in developing countries where hepatitis B and aflatoxin ingestion are prevalent causal exposures (Parkin et al. 1993). In the United States, an estimated 17,300 new cases of liver cancer and 14,400 deaths attributed to this cancer were expected to occur in 2003 (ACS 2003). Liver cancer is more common among men than women, in part reflecting the greater alcohol intake by men. Liver cancer incidence and mortality rates have increased since the 1980s in the United States (McKean-Cowdin et al. 2000). Hypotheses for this increase include the increasing frequency of hepatitis C virus and hepatitis B virus (HBV) infections.

Interpretation of the relationship between smoking and liver cancer is complicated by the potential for confounding by alcohol and HBV infections. First, alcohol intake is an established risk factor and smokers tend to drink more than nonsmokers, and this exposure has not been measured routinely in all studies that include information on smoking history. Second, chronic HBV infections are recognized as a major cause of this malignancy (IARC 1988). As for alcohol, not all epidemiologic studies that have addressed smoking have also assessed the hepatitis status of study participants. Hence, the unconfounded contribution of smoking to risks for liver cancer has been difficult to assess. Considerable epidemiologic evidence indicates, however, that smokers are at an increased risk for this cancer.

Conclusions of Previous Surgeon General's Reports

The 1990 Surgeon General's report (USDHHS 1990) noted an association between smoking and hepatocellular cancer that persisted after controlling for potentially confounding lifestyle factors including alcohol intake. That report also noted that HBV infections may modify the effects of smoking on the risk of liver cancer. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that smoking might be a contributing factor to the development of liver cancer.

Biologic Basis

Circulating carcinogens from tobacco smoke are metabolized in the liver, thus exposing the liver to many absorbed carcinogens. A long-term exposure to these carcinogens may therefore lead to cellular damage in the liver and the development of cancer. Carcinogens may act directly on the genes of the hepatocytes.

Epidemiologic Evidence

Epidemiologic data come from a wide range of studies in both low- and high-incidence countries (Table 2.35). Many of these studies have evaluated smoking, alcohol, and viral causes of liver cancer thoroughly, although some of the larger cohort studies have not controlled for each of these causal agents in assessing smoking's effect. Cigarette smoking was directly related to the risk of liver cancer as the number of cigarettes smoked per day increased in some case-control studies (Yu et al. 1983; Trichopoulos et al. 1987b; Kuper et al. 2000) but not in others (Tanaka et al. 1992).

In a cohort study of U.S. veterans, Hsing and colleagues (1990a) noted a significant trend in increased risks with an increasing number of cigarettes smoked, but their analysis did not control for alcohol consumption or hepatitis viral status. On the other hand, Doll and colleagues (1994) did not observe a trend in risk with higher levels of cigarette smoking in the 40-year report of the British physicians cohort study, and concluded that smoking is not related to liver cancer. In a 12-year cohort study of 14,397 residents of Taiwan aged 40 years and older, cigarette smoking was positively related to mortality from liver cancer (Liaw and Chen 1998). Among men, 110 deaths from liver cancer were identified, and for current smokers the RR was 2.2 (95 percent CI, 1.4–3.6) compared with persons who had never smoked. These authors adjusted for alcohol consumption and the presence of HBV surface antigens.

For persons smoking more than a pack a day, the RR for liver cancer has been 2 or more in both case-control and cohort studies, compared with the risk for persons who had never smoked (Yu et al. 1983; Hsing et al. 1990a; Doll et al. 1994; Kuper et al. 2000). However, not all studies have found an effect of this magnitude (Tanaka et al. 1992; Chiesa et al. 2000; Mori et al. 2000a). This inconsistency may be in part due to the study design and to the relative contribution of HBV infection to the risk of malignancy. For example, Lam and colleagues (1982) observed a RR of 3.3 (95 percent CI, 1.0–13.4) among current smokers, but the association was confined to those who were HBV-negative. Similarly, Trichopoulos and colleagues (1980, 1987b) observed significant associations among HBV-negative persons. In contrast, in a cohort of HBV-positive men and women in China, Tu and colleagues (1985) observed a RR of 4.6. One explanation for the varying results is the dominant role of hepatitis viral infection and the extent to which its effects have been considered in the studies on smoking. The higher RRs that were observed in several studies of persons who were negative for HBV compared with those who were positive suggest that this explanation is plausible.

Evidence Synthesis

A substantial body of epidemiologic evidence supports a relationship between smoking and liver cancer, but a positive association was not found in all studies considered. The metabolism in the liver of the many carcinogens from tobacco smoke leads to an exposure of hepatocytes to these carcinogens. The strength of an association between cigarette smoking and liver cancer varies according to HBV infection status, with stronger associations among those who are negative for HBV. In many of the studies, risk increases with the number of cigarettes smoked per day. Although confounding by alcohol and HBV infection status may bias the findings of some studies, controlling for these causes does not remove the strong association between smoking and liver cancer seen in several of the studies summarized in this report. Finally, in 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the liver (IARC 2002).

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and liver cancer.

Implications

The global burden of liver cancer may increase if smoking increases around the world. Further research is needed to resolve the relationship of smoking to liver cancer with further consideration of the history of hepatitis infection and alcohol use.